

## Review

**Cite this article:** Sharma S, Kohli C, Johnson L, Bennet L, Brusselaers N, and Nilsson PM (2020) Birth size and cancer prognosis: a systematic review and meta-analysis. *Journal of Developmental Origins of Health and Disease* 11: 309–316. doi: [10.1017/S2040174419000631](https://doi.org/10.1017/S2040174419000631)

Received: 28 December 2018  
Revised: 31 May 2019  
Accepted: 23 August 2019  
First published online: 24 October 2019


### Keywords:

Birth weight; cancer; fetal; mortality; neoplasms; prognosis; survival

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# Birth size and cancer prognosis: a systematic review and meta-analysis

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## Abstract

There is an established link between birth parameters and risk of adult-onset cancers. The Developmental Origins of Health and Disease concept provides potential underlying mechanisms for such associations, including intrauterine exposure to endogenous hormones (androgens and estrogens), insulin-like growth factors, etc. However, there is conflicting evidence on the association between birth parameters and the cancer mortality risk. Therefore, we aimed to review and analyse the available data on the association linking birth weight and birth length with cancer mortality. Eleven studies were identified, published until April 2019. A significant association between birth weight and the *prognosis* of cancer (overall) was found (relative risk, RR 1.06, 95% confidence interval, CI: 1.01, 1.11), with low heterogeneity ( $I^2 = 27.7\%$ ). In addition, higher birth weight was associated with poorer *prognosis* of prostate cancer (RR 1.21, 95% CI: 1.02, 1.44). However, the association of birth weight with breast cancer mortality risk in women was not significant (RR 1.16, 95% CI: 0.93, 1.44), which might be due to high statistical heterogeneity ( $I^2 = 67.9\%$ ). Birth length was not associated with cancer mortality risk (RR 1.0, 95% CI: 0.90–1.11). It might be inferred that birth parameters are not associated with cancer mortality as strongly as with the risk of developing cancer. Also, the association between birth parameters and cancer mortality risk is not uniform and varies according to its subtypes, and study characteristics/design. This highlights the need for further prospective studies.

## Introduction

Substantial evidence implicates the crucial role of early life factors in the occurrence of adult-onset diseases, including cancers.<sup>1</sup> The results of many studies suggest that birth parameters, a proxy for cumulative *intrauterine* exposures, are associated with cancer risk in adulthood.<sup>2</sup> These findings are plausibly explained by the Developmental Origins of Health and Disease hypothesis, which suggested that fetal adaptive strategies to the adverse *intrauterine* environment generate long-term consequences for poor health.<sup>3</sup> Birth weight in relation to gestational age is one of the most intensively studied birth parameters in predicting adult cancers' risk.<sup>2,4</sup> Of all the widely prevalent cancers, there are convincing results linking higher birth weight with increased risk of incident breast-, prostate- and testicular cancer.<sup>5</sup>

However, less attention has been given to explore the effects of birth parameters in predicting *prognosis* (survival or mortality) among adult cancer patients. A meta-analysis, determining associations between birth weight and various causes of adult mortality, concluded that there is a strong positive association of birth weight with cancer mortality among men, but not in women. This impressive literature is limited by the bias of incomplete identification of studies, the number of included studies (only five) and the study of birth weight as the only birth parameter.<sup>6</sup> Given that many high-quality articles investigating the potential effect of birth parameters on cancer *prognosis* have not been included in this review, and that there is conflicting evidence on such associations from the existing literature, we conducted the systematic review and meta-analysis. Thus, the aim of this systematic review and meta-analysis was to determine whether birth size is associated with *prognosis* of cancer in adults.

## Research question

Are markers of birth size at delivery (birth weight, birth length and head circumference) related to the *prognosis* of adult-onset cancers?

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## Methods

### Search strategy

We systematically searched MEDLINE (Pubmed), EMBASE and Web of Science from inception until the end of April 2019 to identify observational studies that have reported on associations between birth parameters (birth weight, birth length and head circumference) and *prognosis* of any adult-onset cancer, using overall or cancer-specific mortality as defined by the authors. Besides, reference lists and citation indices of the included studies were also searched. Inclusion was limited to studies, which reported cancer mortality in patients aged more than 20 years. All the studies that met the inclusion criteria were included irrespective of the study site, hospital or community-based settings, or sample size. For meta-analysis, the studies that have reported risk estimates and the confidence intervals (CIs) of the association between birth weight or birth length and adult-onset cancer mortality (overall or specific type) were included. We did not include conference abstracts or unpublished or grey literature, anecdotal reports, or case series, or manuscripts published in any language other than English.

Searches were performed by two reviewers (SS and CK) independently. Keywords used for search engine were ('Birth weight' OR 'Birth size' OR 'Birth parameters' OR 'Birth length' OR 'Gestational age' OR 'Head Circumference') AND (cancer OR neoplasm OR carcinoma OR 'Neoplasms' OR tumor OR tumour) AND ('prognosis' OR survival OR mortality). We included studies of all designs (case-control, cohort, nested case-control, and longitudinal cohort studies). We contacted corresponding authors of two studies, which did not report risk estimates for the associations between birth weight and cancer *prognosis*.

### Data extraction

Two reviewers (SS and CK) independently assessed titles and abstracts to select articles based on *a-priori* established in- and exclusion criteria. In case of discordance between the two reviewers, the consensus was made with the help of other co-authors. All the search results were imported into Endnote (X9.0.1) and duplicates, if any, were removed. In case of overlap of the study population from two or more papers, the most recent one was selected. When multiple studies were published with a substantial geotemporal overlap in the cohort population, the most recent publication was selected.

### Quality assessment

One of the reviewers (SS) performed the quality assessment of the papers using the Newcastle–Ottawa Scale for cohort and case-control studies.<sup>7</sup> The scale uses a star system to evaluate the cohort and case-control studies and a maximum of eight stars could be achieved.

### Statistical analysis

For studies reporting results with categorical birth weight or birth length, we used the most fully adjusted risk estimates and 95% CI for the highest versus lowest reported (reference) category. Hazard ratios and other reported risk ratios were considered interchangeably. For studies reporting results with continuous birth weight or birth length, we used the reported most fully adjusted risk estimates and their CI per unit of increase, respectively, 0.5–1 kg increase in birth weight, or per cm increase in

birth length and their standard errors for all the studies. The pooled and weighted relative risks were calculated using a random effects meta-analytic model, and statistical heterogeneity was assessed by means of the  $I^2$  statistic, with values <50% considered as low statistical heterogeneity. Subgroup analyses were done by cancer type (overall, breast or prostate), exposure (categorical or per unit of increase) and for both sexes separately if feasible.

Publication bias was assessed by generating a funnel plot and assessing its symmetry. Because of the relatively low number of studies, further statistical testing (e.g., Egger's or Begg's test) was considered unreliable. The statistical analyses were performed using Stata version 14 (Stata Corp., College Station, TX, USA).

## Results

The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow chart for the systematic review is shown in Fig. 1, resulting in 11 eligible articles, of which 8 reported the association between birth weight and cancer mortality only, 3 on both birth weight and birth length, and none on head circumference. The main characteristics of these studies are presented in Table 1. All the studies scored six or more stars on the Newcastle–Ottawa Scale. Among 11 studies, there were 7 cohort studies and 4 case-control studies.<sup>8–18</sup> Seven out of 11 studies were cohort-based by design<sup>9–11,13,14,16,17</sup> and 4 were case-control studies.<sup>8,12,15,18</sup> Ten of these 11 included studies used data on birth weight from hospital archives, medical records or registers,<sup>8,9–11,13–18</sup> and 9 studies were from Nordic countries.<sup>8,9,11,13–18</sup> However, only three studies were identified for associations between birth length and cancer *prognosis*.<sup>8,11,15</sup> Two studies were excluded from the meta-analysis because one did not report the risk estimates of the association between birth weight and death due to prostate cancer, and the other did not specify the risk estimate for the mortality due to neoplasms in adulthood.<sup>17,18</sup> The authors of the studies were contacted, however, they did not respond.

The average age at death due to cancers among studies was low (51.5, 58.8 years).<sup>11,14</sup> The median years of follow-up of the cancer cases post-diagnosis ranged between 8 and 11 years in the studies.<sup>13,15,16</sup>

### Birth weight and prognosis of breast cancer

All the studies except one<sup>10</sup> reported poorer breast cancer *prognosis* in individuals with a larger birth weight.<sup>11,12,15,16</sup> However, the associations did not reach statistical significance in all but the study by Sovio *et al.*<sup>16</sup> Two of these studies from Norway and USA were nested case-control studies<sup>12,15</sup> and the remaining studies from Sweden, Finland and England had a cohort study design.<sup>11,16</sup> Birthweight was adjusted for gestational age in two of the five studies.<sup>12,15</sup>

### Birth weight and prognosis of prostate cancer

Of the five studies reviewed,<sup>8,10,11,13,18</sup> all suggested a positive association between larger birth weight and mortality due to prostate cancer, only one of which reached statistical significance.<sup>11</sup> The study by Gerdtsen *et al.* did not show the risk estimates, but revealed that the birth weight was not associated with the mortality due to prostate cancer.<sup>18</sup> Three of the five studies were from different counties in Sweden (Malmö, Gothenburg, and Uppsala)<sup>8,13,18</sup> and the other two were from Finland and England.<sup>10,11</sup> The studies from Sweden together cover a wide range of time period, including individuals born before 1900. Ekblom *et al.* adjusted for a large

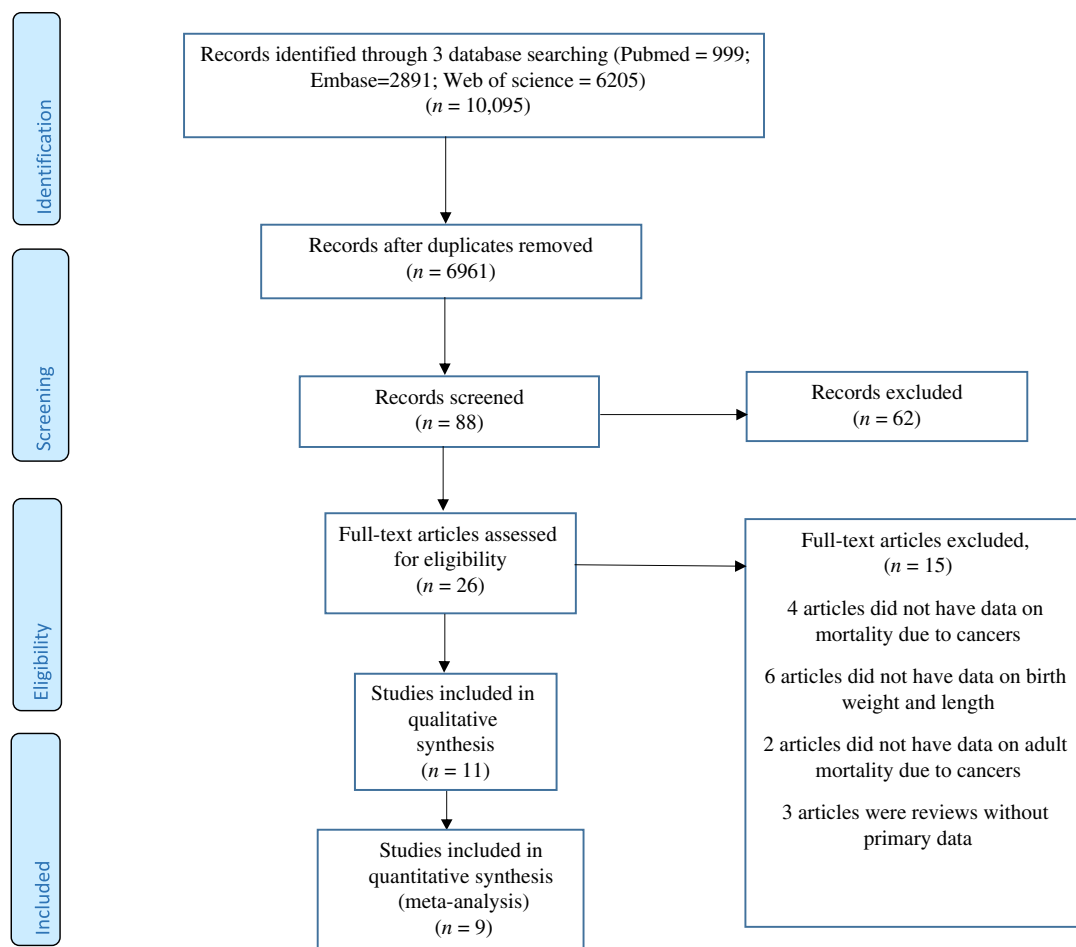


Fig. 1. Flow chart of the identification and screening procedure.

number of confounders including socio-economic status, history of pre-eclampsia in mother, etc.<sup>8</sup> Eriksson *et al.* reported that the association between birth weight and mortality due to prostate cancer is not age-dependent.<sup>13</sup>

### Birth weight and prognosis of cancer (overall)

All four included studies of birth weight and cancer mortality among men and women reported that higher birth weight is associated with increased cancer mortality.<sup>9–11,14</sup> Such associations were statistically significant for men in two of the four studies.<sup>9,10</sup> All the included studies were cohort by design and from different countries (England, Denmark, Sweden, and Finland).

### Meta-analysis of birth weight and cancer mortality

Risk estimates were pooled from nine studies for the risk of mortality from cancers per kg increase in birth weight using the random effects model (Fig. 2). We found that birth weight was associated with a small increased risk of overall mortality (relative risk, RR 1.06, 95% CI: 1.01, 1.11), and the heterogeneity among studies was low ( $I^2 = 27.7\%$ ). Further, subgroup analyses of the cancer types (breast and prostate cancers) showed different associations with varying amounts of heterogeneities. Higher birth weight was associated with a 21% increased risk of prostate cancer mortality (RR 1.21, 95% CI: 1.02, 1.44) and the heterogeneity was low ( $I^2 = 15\%$ ). On the contrary, the association of birth weight with

breast cancer was not significant (RR 1.16, 95% CI: 0.93, 1.44), with a high amount of heterogeneity ( $I^2 = 67.9\%$ ).

### Birth length and prognosis of cancers

The relationship between birth length and cancer mortality was not uniform across studies.<sup>8,11,15</sup> Moreover, the association was statistically significant only in one of the three studies.<sup>15</sup> Maehle *et al.* in his study suggested that higher birth length was associated with poorer prognosis of breast cancer.<sup>15</sup> The three studies were from different Nordic countries (Finland, Sweden and Norway).

### Meta-analysis of birth length and cancer mortality

We separately conducted a meta-analysis of the three studies for mortality per cm increase in birth length (Fig. 3). We found that birth length was not associated with cancer mortality (RR 1.0, 95% CI: 0.90, 1.11), which might be due to the fact that the unit of increase may be too small to have sufficient power to detect a difference.

Visual inspection of the funnel plot did not provide evidence of small study effect (publication bias; Supplementary figure S1, and S2). Further, subgroup analysis based on sex (Fig. 4) revealed that the association of birth weight with cancer mortality risk (overall) was stronger and significant for men (RR 1.11, 95% CI: 1.00, 1.24) compared to women (RR 1.01, 95% CI: 0.95, 1.07). Subgroup analysis based on the type of birth data reported (categorical or

**Table 1.** Characteristics of included studies on birth weight or birth length in relation to cancer mortality ( $n = 11$ )

First author	Publication year	Study country	Study design	BW source	Birth cohort	Year of follow-up	Cancer type	Case number (deaths)	Control number	Unit of risk measurement	Exposure measure	Published association for BW/BL with 95% CI	Adjustment for covariates
Ekbom <i>et al.</i> <sup>8</sup>	1996	Sweden (Uppsala)	Nested case-control	Standardized hospital chart	1874–1946	1958–1994	Prostate cancer	80	196	OR	Per 500 g for BW and per 20 mm for BL	OR per 500 g BW increase: 1.22 (0.87–1.70) OR per 20 mm BL increase: 0.91(0.68–1.21)	Matched by birth year and age at dx.*
Leon <i>et al.</i> <sup>9</sup>	1998	Sweden (Uppsala)	Cohort	Hospital records	1915–1929	1915–1995	All neoplasms	M:599W:480	NA	RR	1 Kg	RR per 1 kg BW increase: M: 1.13 (0.96–1.33) W: 1.04 (0.87–1.24)	Adjusted for period of birth as a three-level categorical variable (19159, 19204, 19259).
<sup>b</sup> Syddall <i>et al.</i> <sup>10</sup>	2005	England (Hertfordshire)	Cohort	Ledgers	1911–1939	1951–1999	All neoplasms	M:1867W:1049	NA	HR	1 SD	HR per 1SD score of BW increase: M:1.06 (1.02–1.11) W:1.01 (0.95–1.07)	Adjusted for year of birth
<sup>c</sup> Kajantie <i>et al.</i> <sup>11</sup>	2005	Finland (Helsinki)	Cohort	Hospital records	1924–44	1971–1998	All cancers	M:361 (BW); 357(BL) W:269 (BW); 267 (BL)	NA	HR	1 Kg for BW and 1 cm for BL	HR per 1 Kg BW decrease: M:0.76 (0.61–0.95) W:1.09 (0.82–1.43) HR per 1 cm decrease in BL: M:0.97 (0.91–1.03) W:1.06 (0.99–1.14)	Adjusted for birth years and gestational age
Sanderson <i>et al.</i> <sup>12</sup>	2006	USA	Case-control	Self-reported	1944–1947	1983–2002	Breast cancer	W:279	739 alive out of 1024 cases	HR	>2500, 2500–3999, >4000 g	HR of BW > 4000 g over ref BW < 2500 g 1.80 (1.0–3.10)	Adjusted for age at diagnosis, diagnosis year, stage of diagnosis and birth order
Eriksson <i>et al.</i> <sup>13</sup>	2007	Sweden (Gothenburg)	Cohort	Obstetrics records	1913	1963–1998	Prostate cancer	M:68	NA	CR	1 kg	CR per 1 kg BW increase 1.41(0.93–2.12)	Adjusted for the birthyear and age

Baker <i>et al.</i> <sup>14</sup>	2008	Denmark (Copenhagen)	Cohort	Copenhagen school health record register	1936–1979	1968–2004	All cancers	M: 2110 W: 2335	NA	HR	2000–2150, 2151–3250, 3251–3750, 3751–4250, 4251–5500	HR of BW 4251–5000 g over ref BW 2000–2150 g: 1.12 (0.99–1.28)	Adjusted for the birth year
Maehle <i>et al.</i> <sup>15</sup>	2010	Norway	Case-control	Birth archives from clinics and hospital	1910–1970 (for both Bergen and Trondheim)	Bergen: 1959–2003 Trondheim: 1959–1999	Breast cancer	W: 87	244 alive out of 331 cases	HR	For BW: 1st quintile: ≤3050 g, 2nd–4th quintile: 3051–3850 g, 5th quintile: >3850 g For BL: <48 cm and >52 cm	HR of BW > 3850 g over ref BW ≤ 3050 g: 1.16(0.59–2.29) HR of BL > 52 cm over ref BL < 48 cm: 1.83 (1.03–3.25)	Adjustment for place of birth and year of diagnosis
Sovio <i>et al.</i> <sup>16</sup>	2013	Sweden (Uppsala)	Cohort	Uppsala birth cohort	1915–1929	1958–2010	Breast cancer	W:171 women died due to breast cancer out of 311 deaths	NA	HR	1 SD	HR for 1 SD (BW for GA) increase: 1.27(1.09–1.47)	Adjusted for gestational age and other factors <sup>a</sup>
Wennerström <i>et al.</i> <sup>17</sup>	2015	Denmark	Cohort	Civil Registration System	1979–2011	1979–2011	All cancers	1813	NA	HR	SGA:≤10th percentile,Normal: 11th–89th percentile,LGA: ≥90th percentile	-----	Adjusted for gestational age
Gerdtsen <i>et al.</i> <sup>18</sup>	2015	Sweden (Malmö)	Nested case-control	Hospital charts and archives	MPP:1921-1949 MDCS: 1923–1945	MPP: 1974–2006, MDCS: 1991–2006	Prostate cancer	159	636	OR	1 kg	-----	Matched by birth year and age at diagnosis

BW, Birth weight; BL, Birth length; CI, Confidence interval, CR: Crude rate; G, Grams; GA, Gestational age; HR, Hazard ratio; kg, Kilogram; LGA, Large for gestational age; M, Men; MPP, Malmö Preventive Project; MDCS, Malmö Diet Cancer Study; NA, Not applicable; OR, Odds ratio; RR, Rate ratio; ref, Reference; SGA, Small for gestational age; SD, Standard deviation; W, Women

<sup>a</sup>Also adjusted for maternal age, socio-economic status, parity, pre-eclampsia, eclampsia, prematurity, age at menarche and neonatal jaundice

<sup>a</sup>Other factors included birth length, age at first child, number of children, adult occupational social class in 1960, educational level at 1970 and personal income at 1970

<sup>b</sup>Additionally for cancer-specific estimates: prostate cancer ( $n = 125$  deaths); HR (95% CI) per 1 SD score of BW increase: 1.12 (0.95, 1.32) and breast cancer ( $n = 284$  deaths); HR (95% CI) per 1 SD score of BW increase: 0.95 (0.85–1.07)

<sup>c</sup>Additionally for cancer-specific estimates: prostate cancer ( $n = 22$  deaths); HR (95% CI) per 1 kg BW decrease: 0.42 (0.17, 1.01) and breast cancer ( $n = 70$  deaths); HR (95% CI) per 1 kg BW decrease: 0.93 (0.54–1.59)

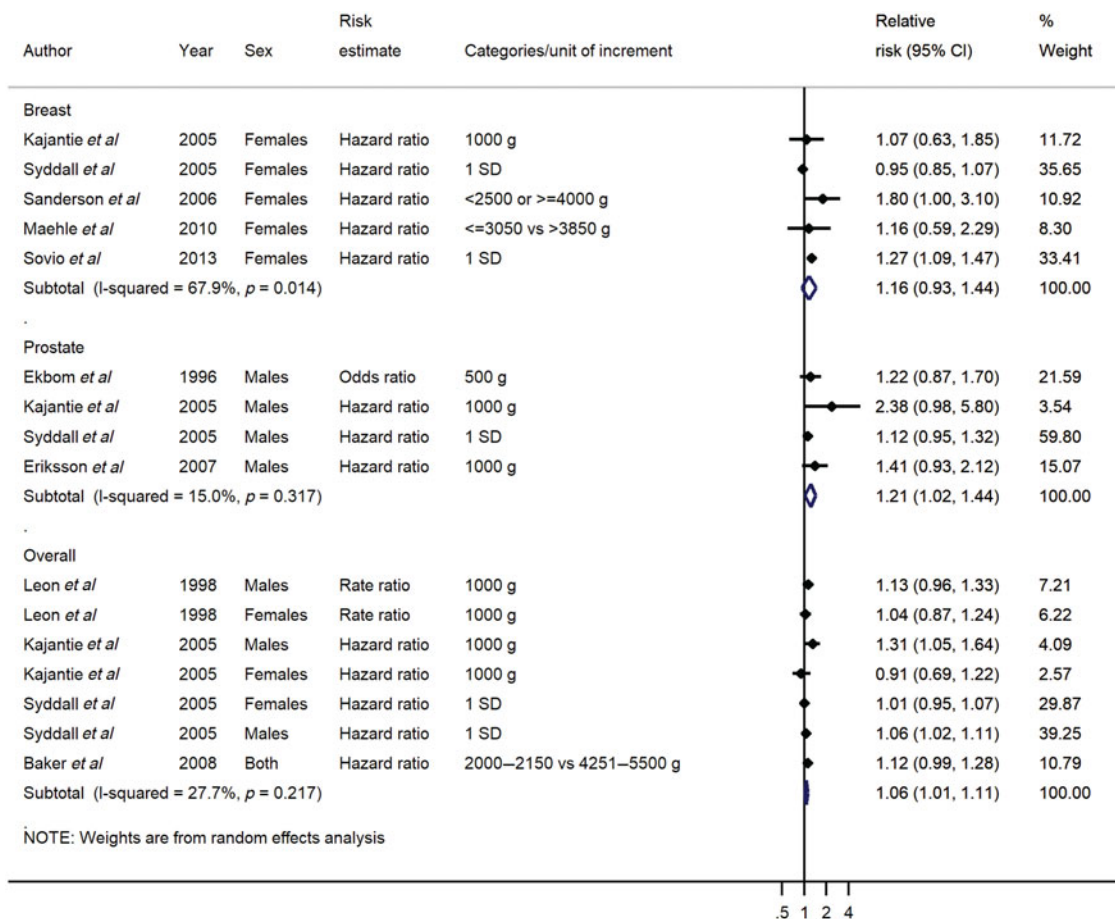


Fig. 2. Birth weight (per kg) in relation to risk of cancer mortality (overall (n = 4), prostate (n = 4) and breast (n = 5)) using a random effects model.

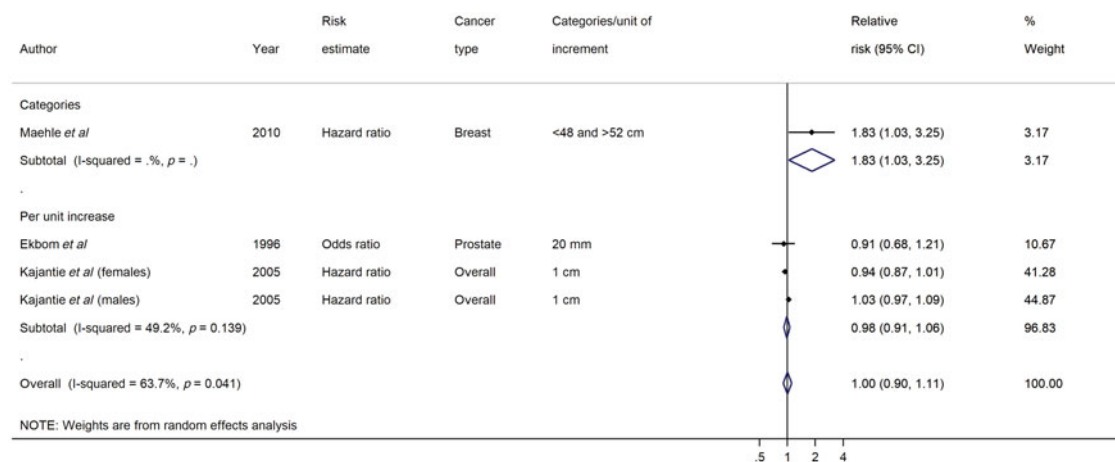


Fig. 3. Birth length (per cm) in relation to risk of cancer mortality (overall (n = 1), prostate (n = 1) and breast (n = 1)) using a random effects model.

continuous variable) did not significantly change the heterogeneity or summary risk estimates (Supplementary figure S3 and S4).

**Discussion**

This systematic review and meta-analysis included data on nearly 9601 adult deaths among some 311,970 individuals. Our study suggests that higher birth weight is associated with an increased cancer

overall mortality. The association of birth weight with cancer mortality risk was stronger for prostate compared to breast cancer. Birth length has not been found to be associated with cancer mortality.

The results are compatible with the findings from another meta-analysis of five studies relating birth size with cancer mortality.<sup>6</sup> The study suggested 13% increased risk of mortality due to cancers (Hazard Ratio, HR 1.13, 95% CI: 1.07,1.19) for



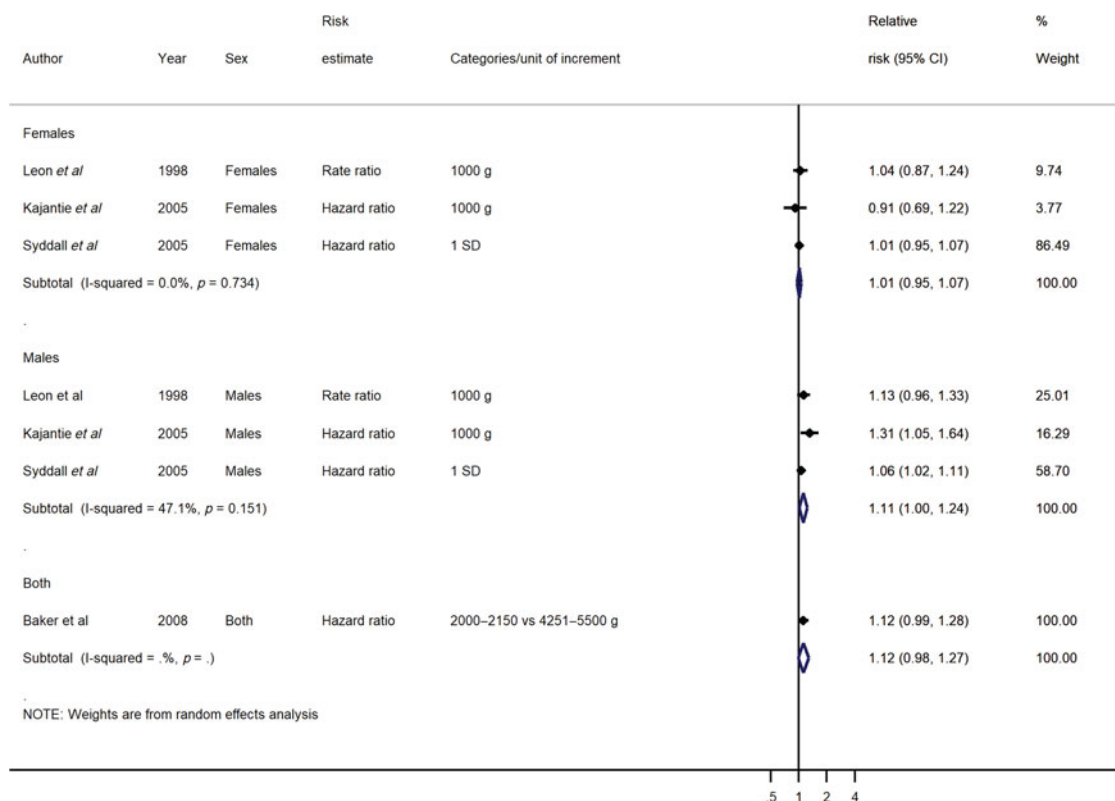


Fig. 4. Birth weight in relation to risk of cancer mortality segregated by sex using a random effects model.

men and 4% increased risk (HR 1.04, 95% CI: 0.98, 1.10) among women ( $P_{\text{interaction}} = 0.03$ ).<sup>6</sup> Contrary to our findings, Belbasis *et al.* observed no convincing evidence supporting association between high birth weight and later health outcomes, including cancers. Instead, they suggested the associations of low birth weight with increased risk for all-cause mortality.<sup>2</sup>

Our findings and the results from a meta-analysis by Zhou *et al.* on prostate cancer risks (2015) together suggest the hypothesis that higher birth weight is a risk marker in the entire trajectory of prostate cancer, from incidence to metastasis to mortality.<sup>19</sup> The study provided evidence that heavier birth weight may be associated with modest increased risks of total and aggressive/lethal prostate cancer.<sup>19</sup> The differential associations of birth weight with the risk of cancer mortality (overall) and the mortality of its subtypes highlight that the relationship is not uniform across cancers. Prostate and breast cancers are among the few cancers, which have been studied extensively for their relations with birth parameters.<sup>5</sup> It has been established that higher birth weight and birth length are associated with an increased risk of prostate and breast cancer incidence. However, the associations of birth parameters with cancer prognosis are not as strong and significant compared to their associations with cancer incidence.<sup>19,20</sup>

It is well known that birth weight and gestational age are highly correlated.<sup>2</sup> Despite that, a few studies have adjusted birth weight for gestational age while assessing associations with cancer mortality risk.<sup>11,16,17</sup> In addition, only a few studies have adjusted for socio-economic factors,<sup>16</sup> which are potential confounders linked with both exposure (birth weight) and the outcome (cancer mortality).<sup>21</sup> Some of the studies have a very long period of

follow-up of the cancer cases post-diagnosis, which minimises the bias of missing potential cases because cancer-related mortalities occur late in life. This provides an advantage over studies with a shorter period of follow-ups.<sup>22</sup>

The sex-segregated analysis reveals stronger and significant association of birth weight with cancer mortality risk among men than women. This is in agreement with the findings from a study by Risnes *et al.*, which reported stronger positive associations for men than women. In addition, significant association of birth weight with prostate cancer risk compared to breast cancer risk in our results supports this statement.<sup>6</sup> Although multiple studies have shown associations between head circumference and the risk of brain, breast and colorectal cancer incidence,<sup>23,24</sup> we did not find any study assessing the association with cancer survival.

The strength of our study includes thorough systematic search of the studies and addition of a novel research to the literature. Our meta-analysis has several limitations. Firstly, there was a moderate amount of heterogeneity among studies as a result of which a definitive association could not be concluded. This could be due to different study designs, and different outcomes of the study (overall cancer mortality or specific cancer mortality). Secondly, we used the published, aggregated risk estimates and our meta-analysis was not based on individual participant data (IPD). IPD allow more powerful and uniformly consistent analyses as well as better characterisation of subgroups and outcomes, compared to those which are based on aggregate data extracted from published risk estimates.<sup>25</sup> All the studies in our analysis were from high-income countries, which limit the generalisability of the results. Despite clinical and methodological heterogeneity, statistical heterogeneity was limited,

and associations were found between birth weight and cancer prognosis. However, residual confounding cannot be ruled out, and the findings may not be generalised to less highly developed countries. Lastly, we could not exclude the possibility of publication bias, given that only nine studies published results for the associations between birth size and risk of cancer mortality.

In conclusion, the systematic review and meta-analysis suggest that higher birth weight is associated with increased overall cancer mortality and prostate cancer mortality. The effect of birth weight on the risk of mortality due to breast cancer is not convincing. This suggests the need for prospective studies and elaborative research on birth cohorts for conclusive results on such associations.

**Supplementary material.** To view supplementary material for this article, please visit <https://doi.org/10.1017/S2040174419000631>

**Acknowledgements.** None.

**Financial Support.** This review was supported by a grant from the Research Council of Sweden to PM. Nilsson.

**Conflicts of Interest.** None.

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